

PHARMACOLOGY.—*The toxicity of sodium cyanide and the efficiency of the nitrite-thiosulphate combination as a remedy for poisoned animals.*¹ A. B. CLAWSON, JAMES F. COUCH, and H. BUNYEA, Bureau of Animal Industry.

The poisonous qualities for sheep of potassium cyanide and of hydrocyanic acid have been discussed briefly in former papers and the results that may be expected by treating the poisoned animals with sodium nitrite and sodium thiosulphate in combination have been pointed out.² More recently the writers have had an opportunity of testing the toxicity of sodium cyanide for sheep and the nitrite-thiosulphate combination as a remedy for animals poisoned by it. It is proposed in this paper to present the results of tests with sodium cyanide and briefly to compare them with similar results obtained in the experimental work with potassium cyanide and with hydrocyanic acid. Such a comparison seems especially fitting as the animals used in the experiments with the different cyanides had been subjected to very similar conditions and during the respective investigations were handled in the same way.

TOXIC AND LETHAL DOSES OF SODIUM CYANIDE

In determining the toxic and lethal doses of sodium cyanide, when administered as a drench in a water solution, 17 experimental tests were made on 14 sheep. The dosages and results are shown in table 1.

TABLE 1.—QUANTITIES OF SODIUM CYANIDE GIVEN TO SHEEP IN A DRENCH AND THE EFFECTS PRODUCED WHEN NO REMEDIES WERE USED.

Date 1935	Sheep		Quantities ^a given and effects produced		
	No.	Weight kg.	Symptoms	Sickness	Death
Jan. 19	1457	34.92			34.66
19	1453	36.73			34.30
19	1482	38.55			32.69
19	1474	37.64			13.95
14	1467	53.06			5.78
14	1471	31.75			5.56
16	1472	39.91			5.32
18	1479	29.02			5.28
14	1468	42.63			5.22
18	1453	36.73		5.20	
18	1476	37.64			5.19
16	1466	35.83		5.10	
18	1469	43.99			4.92
16	1454	46.49	4.82		
14	1466	35.83	4.63		
16	1453	36.73	4.57		
16	1455	30.84	4.15 ^b		

^a The quantities are given as milligrams of sodium cyanide per kilogram of animal's weight.

^b Symptoms very mild, consisting only of a stimulation of the respiration.

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One sheep was used three times and one was used twice. Each of the other animals was used in a single experiment. In 7 additional cases a solution of 1 gram of sodium nitrite and 2 grams of sodium thiosulphate in 15 c.c. of water was injected intraperitoneally at periods ranging between 1.5 and 4 minutes after the cyanide was administered. These are shown in table 4.

The sodium cyanide solution was carefully prepared and checks made so that each c.c. of solution contained 21.003 mg. of sodium cyanide equal to 11.147 mg. of the cyanide radical (CN), or the equivalent of 11.575 mg. of HCN.

In all cases the dosages were computed as milligrams of sodium cyanide per kilogram of animal weight.

As shown in table 1, a quantity of sodium cyanide equivalent to 4.15 mg. per kg. of animal weight was the smallest dose given. As the effects were very slight, consisting of a mild stimulation of the respiration, and as somewhat larger doses gave correspondingly more marked results, this quantity (4.15 mg. per kg.) is evidently very close to the minimum toxic dose.

The minimum lethal dose is somewhat in doubt, but evidently is close to 5.22 mg. per kg. of animal weight. Sheep 1468, the animal killed by this quantity; sheep 1479, killed by 5.28 mg., and sheep 1476, killed by 5.19 mg., had received no previous drenchings of cyanide. As compared with these, sheep 1453 made sick by 5.20 mg., had been poisoned three times previously by cyanide, the last time on January 17, when it had been given 3 m.l.d. of hydrocyanic acid, followed by an intraperitoneal injection of the nitrite-thiosulphate combination, and sheep 1469 which died following the administering of 4.92 mg. had been given two previous doses of 3 m.l.d. each of hydrocyanic acid, followed by the nitrite-thiosulphate combination. It is possible, although not clear, that the previous treatment may have somewhat modified the results. It is evident that the m.l.d. does not exceed 5.22 mg. per kg. of animal weight.

COMPARATIVE TOXICITY OF CYANIDE WHEN GIVEN IN DIFFERENT FORMS

For comparison with potassium cyanide and hydrocyanic acid, the minimum toxic and minimum lethal doses are given in table 2. In this table the dosages are given in terms of the substances actually administered and of the cyanide radical (CN) equivalents.

Based on the smallest quantities of the substances themselves that produced visible effects, hydrocyanic acid, potassium cyanide, and

TABLE 2.—RELATIVE QUANTITIES^a OF KCN, HCN AND NaCN REQUIRED, WHEN GIVEN AS A DRENCH, TO PRODUCE SYMPTOMS IN AND TO KILL SHEEP.

Substance given	Minimum toxic dose		Minimum lethal dose	
	As substance given	As CN equivalent	As substance given	As CN equivalent
HCN	1.05	1.01	2.29	2.20
KCN	2.43	.95	5.57	2.23
NaCN	4.15	2.20	5.22	2.77

^a Dosages given as milligrams per kilograms of animal weight.

sodium cyanide bear the approximate relationship represented by the values 1:2.3:4. That is, sodium cyanide is one-half as toxic as the potassium salt and one-fourth as toxic as hydrocyanic acid. If considered on the basis of their cyanide equivalents, their ratio is 1:1:2.2.

The ratios for the minimum lethal dose are somewhat different, being 1:2.4:2.3, when based on the substances actually administered, and 1:1:1.26, if based on the cyanide equivalent. Apparently sodium cyanide is less poisonous than either hydrocyanic acid or potassium cyanide, while there is no appreciable difference between the two latter forms.

The relationship between minimum toxic and minimum lethal doses of the three forms differ somewhat. For hydrocyanic acid and potassium cyanide the relationship is nearly the same, it being approximately 1:2 in both cases. For sodium cyanide it is close to 1:1 $\frac{1}{4}$. That is, with HCN and KCN, about twice as much is required to kill as to produce visible effects, while with sodium cyanide the lethal dose is only about 25 per cent greater than the minimum toxic dose.

As the efficiency of any remedial measures in cyanide poisoning is closely related to the promptness with which it is given, or, more correctly, the stage of illness when it is administered, a comparison of the rates at which the stages of poisoning develop when the different forms of cyanide are administered is of considerable interest. The various stages overlap so that no actual sharp boundary exists between them. In most cases, however, three points could be determined fairly closely. These are: (1) symptoms, or the time when the respiratory movement began to show the effect of stimulation; (2) collapse, or when the animals fell and were unable to get to their feet; and (3) death. Considering the cases in which fairly accurate observations were obtained, and eliminating such as were influenced by the administration of remedies, averages, times between the giving of the cyanide and the appearance of the effects, were obtained. These are shown in table 3.

TABLE 3.—SHOWING THE TIME FROM THE GIVING OF CYANIDE IN THE THREE FORMS (HCN, KCN, AND NACN) AND VARIOUS EFFECTS.

Form in which given	Effect	No. of cases	Time to effect					
			Minimum		Maximum		Average	
			Min.	Sec.	Min.	Sec.	Min.	Sec.
Hydrocyanic acid	Symptoms	28		20	2			50
	Collapse	23		50	51	30	5	52
	Death	11	12	30	51	46	30	16
Potassium cyanide	Symptoms	79		30	3	00	1	7
	Collapse	80		30	23	00	2	46
	Death	13	6	00	56	00	25	49
Sodium cyanide	Symptoms	24		30	1	45	1	00
	Collapse	18		30	9	50	2	59
	Death	11	8	00	90	00	34	39

Although table 3 is based on too small a number of cases for positive conclusions, it furnishes certain information. The form in which the cyanide is administered as a drench in water solution has no significant influence on the time it takes symptoms to develop. Apparently the time to collapse is somewhat longer when hydrocyanic acid has been given than when potassium or sodium cyanide has been administered. However, the average time in the hydrocyanic acid cases is in part due to two animals that appear to have been unusually resistant. One of these collapsed after $24\frac{1}{2}$ minutes and one after $51\frac{1}{2}$ minutes. With these eliminated the average time was 3 minutes 33 seconds. Of the 23 cases, 17 (or 75 per cent) collapsed in 3 minutes or less. Following the administration of potassium cyanide there were likewise two prolonged cases, one lasting 19 minutes, and one $23\frac{1}{2}$ minutes before collapse. Without these, the average time is 2 minutes 17 seconds. Of the 80 cases 80 per cent collapsed in 3 minutes or less. With sodium cyanide the average is essentially the same as for the potassium cyanide cases. Of the 18 cases, 13 (or 72 per cent) collapsed in 3 minutes or less.

Taking all facts into consideration, it is not apparent that any essential differences exist in the rate at which illness develops following the administration of the three forms of cyanide under consideration. If any one of the substances acts more slowly than the others, it is the hydrocyanic acid.

THE EFFECTIVENESS OF THE REMEDY USED

As previously stated, 7 animals that had received sodium cyanide were treated with the nitrite-thiosulphate combination. Each animal

was injected intraperitoneally with 15 c.c. of a solution containing 1 gram of sodium nitrite and 2 grams of sodium thiosulphate, the two solutions being mixed just before being injected. The quantities of sodium cyanide given these animals varied from 2.5 to 3.15 times the m.l.d. The remedy was administered in from 1½ minutes to 4 minutes after the cyanide. The results are shown in table 4.

TABLE 4.—SHOWING THE EFFECTS OF THE NITRITE-THIOSULPHATE COMBINATION ADMINISTERED INTRAPERITONEALLY AS A REMEDY FOR SHEEP POISONED BY SODIUM CYANIDE

Date 1935	Sheep		Dose m.l.d.	Time in minutes from giving drench of NaCN to			Result
	No.	Weight kg.		Symptoms	Collapse	Giving remedy	
Jan. 18	1482	38.55	2.5	0.75	3.25	3.75	Recovery
18	1480	47.62	2.75	1.00	1.75	1.50	Death
18	1481	42.63	2.75	1.5	2.25	2.25	Death
18	1457	34.92	3.00	1.0	3.72	4.00	Recovery
18	1477	41.72	3.00	0.5	1.75	3.25	Death
18	1478	38.55	3.00	1.0	2.5	3.00	Recovery
16	1473	40.82	3.15	0.75	1.00	2.00	Recovery

Four of the 7 cases, including 3 of the 4 given 3 m.l.d. of sodium cyanide recovered. As shown by the few cases the nitrite-thiosulphate combination is as effective against sodium cyanide as against potassium cyanide³ poisoning, but apparently somewhat less effective than against hydrocyanic acid.⁴

SUMMARY

When given to sheep as a drench in water solution, 4.15 mg. of sodium cyanide per kg. of animal weight produced symptoms of poisoning and 5.22 mg. or more killed, and these quantities are considered to be the approximate minimum toxic and minimum lethal doses, respectively.

Basing the doses on the CN content, sodium cyanide is somewhat less toxic than potassium cyanide or hydrocyanic acid.

Following the administration of sodium cyanide the average time to the appearance of symptoms is approximately 1 minute, to collapse 3 minutes, and to death 34½ minutes. Taking into account the probability of experimental error, these respective periods are about the same as for poisoning by potassium cyanide or by hydrocyanic acid.⁴

The nitrite-thiosulphate combination was effective in 57 per cent of the cases in which it was tried.

³ This JOURNAL 24: 528-532. 1934.

⁴ This JOURNAL 25: 272-276. 1935.